

EDITORIAL COMMENT

Strain Imaging in Uncomplicated Type 1 Diabetes Patients for Risk Stratification

It Ain't as "Sweet" as it Sounds*

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Safety, reliability, ease of use, and relatively low cost has placed echocardiography at the forefront of imaging modalities utilized in the assessment of cardiac function. Over the last 2 decades, techniques to detect pre-clinical cardiac dysfunction, such as the echocardiographic estimation of myocardial strain and strain rate, have been developed. Myocardial strain measures the deformation of tissues in response to stress (1), and speckle tracking echocardiography (STE) has emerged as the preferred method to estimate strain (2-4). In an effort to determine the clinical utility of STE, the prognostic importance of strain has been assessed in a variety of clinical scenarios. Global longitudinal strain (GLS), as derived from STE, has been shown to be an independent and superior predictor of mortality when compared with "traditional" measures of systolic function, such as left ventricular (LV) ejection fraction or wall motion score index (5,6).

Both type 1 and type 2 diabetes mellitus (DM) represent a multisystem disorder associated with substantial cardiovascular morbidity and mortality. Despite being an area of intensive research, the pathophysiology driving the disease process in patients with type 1 DM remains poorly understood, and the approach to management has generally followed

that of patients with type 2 DM, who represent a much larger cohort. Accordingly, the application of strain imaging to define pre-clinical ventricular dysfunction and predict outcomes in both type 1 and 2 diabetes has garnered much interest.

SEE PAGE 400

In this issue of *iJACC*, Danish investigators present the findings of the large, cross-sectional Thousand & 1 study (7). They performed STE to measure GLS in 1,065 patients with type 1 DM *without known heart disease* and compared these values with 198 age- and sex-matched control subjects. The authors presented multiple statistical models to validate the results. In the unadjusted univariate model, there was a significant difference in strain between type 1 diabetic patients and control subjects. However, after adjustment for relevant cardiovascular risk factors and medications in the multivariable model, there was no significant difference in GLS between type 1 diabetic patients and control subjects. Patients were also stratified by the degree of albuminuria, a known risk factor for the subsequent development of heart failure (8). Univariate analysis demonstrated that GLS was significantly different between control subjects and patients with albuminuria, defined as microalbuminuric if the urinary albumin excretion rate was between 30 and 300 mg/24 h and macroalbuminuric if the urinary albumin excretion rate was >300 mg/24 h. Importantly, there was no significant difference in GLS between the normoalbuminuria and control groups. These results did not change significantly on multivariable analysis after adjustment for other relevant factors (7).

To our knowledge, this study is the largest assessing myocardial strain in the diabetes setting. This is a time-consuming and challenging endeavor

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and the authors should be commended and congratulated for this undertaking. What insights, then, are provided by these findings? In contrast to the uncomplicated type 1 DM patients, who demonstrate normal cardiac function in this study, there is a large body of data demonstrating subclinical LV dysfunction as manifested by a reduction in GLS in patients with type 2 DM despite normal LV ejection fraction—both with and without microalbuminuria (2,9). How can we reconcile these important differences?

Although type 1 and 2 DM are diagnosed by the same criteria (10), the underlying pathophysiology of cardiac dysfunction in the 2 diseases is vastly different (11). Type 1 diabetes is the result of an absolute deficiency of insulin, primarily as a result of beta cell failure due to autoimmune mediated destruction. Type 2 diabetes, on the other hand, occurs secondary to a variety of pathophysiological mechanisms, including insulin resistance and beta cell failure, typically in association with a number of cardiovascular comorbidities, including obesity, hypertension, and lipid abnormalities. The mechanisms leading to insulin resistance and beta cell failure remain complex, but involve abnormal hepatic, skeletal, lipid, and cardiac metabolism. Cardiac and beta cell dysfunction occur as a result of impaired calcium homeostasis, activation of the renin-angiotensin system, altered substrate metabolism, and mitochondrial dysfunction. Not only do type 1 and 2 DM differ in pathophysiology, but the response to anti-hyperglycemic therapy differs markedly. Early and adequate replacement of insulin with tight glycemic control has been highly effective in reducing the complications (including macrovascular cardiovascular complications) of type 1 diabetes. Conversely, intensive blood glucose lowering in patients with

type 2 diabetes has been less successful in reducing macrovascular cardiovascular complications of diabetes (12). Not surprisingly, then, these differing pathophysiological mechanisms may lead to different patterns of clinical presentation, subclinical cardiac dysfunction, and response to therapy (Table 1).

Although in the absence of albuminuria, subclinical systolic function may vary between type 1 and 2 DM, the finding that patients with type 1 DM and albuminuria (either micro or macro) demonstrate abnormal GLS is entirely consistent with the published data. DM and microalbuminuria has been shown to herald the development of heart failure (13), and agents that modify albuminuria, such as inhibitors of the renin-angiotensin system, have been shown to reduce heart failure hospitalization (8,14). Albuminuria is regarded as a marker for widespread endothelial damage, and it likely reflects disease in both the cardiac microvascular and coronary macrovascular beds—thus, leading to both cardiomyocyte dysfunction and coronary artery disease.

What are the “take home” messages from this study and the published data regarding strain and diabetes? First, despite similar diagnostic criteria, patients with type 1 and 2 DM represent different cohorts in terms of disease pathophysiology, progression, appropriate therapeutic intervention(s), and response to therapy. Second, microalbuminuria appears to be a robust marker for the presence of subclinical LV dysfunction in patients with type 1 DM and affects patient management (15); therefore, the incremental benefit for strain imaging in this cohort is not clear. Third, although microalbuminuria is associated with subclinical LV dysfunction in this patient cohort, it fails to give any formal insight into disease pathophysiology by which a specific intervention can

TABLE 1 Comparison of Type 1 and 2 DM

	Type 1 DM	Type 2 DM
Age at onset	Predominantly young	Predominantly middle aged and elderly
Etiology	T-cell mediated autoimmune beta cell destruction	Insulin resistance/beta cell failure
Degree of insulin resistance	+	+++
Obesity	+	+++
Association of glycemic control to CVD	+++	+++
Effect of tight glycemic control on macrovascular complications	++	+
Relative association of CVD risk factors with CVD events (high LDL, smoking, HT)	LDL + HT +++ Smoking ++	LDL +++ HT ++ Smoking ++
Microalbuminuria and risk of heart failure	+++	+++

+ to +++ represents the strength of association from lowest to highest.
CVD = cardiovascular disease; DM = diabetes mellitus; HT = hypertension; LDL = low density lipoprotein.

further modify cardiac and/or renal outcomes. Finally, this study confirms the current strategy of cardiovascular protection for patients with type 1 diabetes, as it demonstrates preserved systolic and diastolic function in a large cohort of intensively-treated patients. Future research is required to assess whether novel interventions over and above renin-angiotensin system inhibition can improve outcomes in patients with albuminuria. However, it is vitally important that separate studies are performed

depending upon the etiology of diabetes, as the outcomes may be very different between patients with type 1 or 2 DM.

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